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REVIEW

Epidemiology of Hepatitis B and Associated Liver Diseases in China

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Abstract Hepatitis B virus (HBV) infection has long been a critical public health challenge in China. National surveys revealed a prevalence of approximate 10% for chronic HBV infection in general population. HBV has been the leading cause of chronic hepatitis, cirrhosis, and liver cancers in Chinese population and a common pathogen of acute viral hepatitis. Meanwhile, the epidemic provided important opportunities to research the natural history, public health impact, and therapeutic and preventive interventions for HBV in China. In this review, we summarized the selected key epidemiological studies since 1970s regarding HBV infection and its associated liver diseases in China, and provided considerations for future research, prevention and treatment of HBV.

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HEPATITIS B virus (HBV) is a major public health threat worldwide, leading to millions of death from its associated liver diseases globally each year. Although acute hepatitis is common after infections among adults, it is chronic liver diseases, mainly cirrhosis and hepatocellular carcinoma (HCC), the main contributors of disease burdens caused by HBV. China is among the countries with highest HBV carrier prevalence, and therefore suffers from the greatest impact of HBV and chronic liver diseases. National surveys conducted since

the 1970s have repeatedly showed high prevalence of chronic HBV infection in general population.¹ Epidemiological studies have been carried out to evaluate HBV as the leading pathogen for chronic hepatitis, cirrhosis, and liver cancers in Chinese population as well as for acute viral hepatitis.¹ As more Chinese are diagnosed with rheumatic diseases and malignancies requiring immunosuppressive therapy which could induce flares of HBV, the disease burden associated with HBV may further increase. To address this challenge, national programs have been implemented to initiate and scale up vaccination and treatment coverages. Currently, few works have been published to provide a comprehensive review of the key epidemiological studies on HBV and its associated liver diseases in

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China. To make up this gap, we conducted extensive literature search on both Chinese and English literatures, and interviewed experts on selected topics where published data are scarce. The purpose of this review is to summarize existent epidemiological studies on HBV infection and its associated liver diseases in China. It begins with seroprevalence surveys in general population, which is followed by acute hepatitis B, chronic liver diseases, and HBV transmission, and is concluded by a summary and a comment on further directions.

National seroprevalence surveys

To date, three national HBV seroprevalence surveys have been conducted, in 1979, 1992, and 2006, which provide the most comprehensive information regarding HBV seromarkers in China.^{2,3} These surveys were conducted with proper sampling methods to represent the general population, and used different laboratory methods: reverse passive hemagglutination assay in 1979, solid phase radioimmunoassay in 1992, and enzyme-linked immunosorbent assay in 2006. The national prevalence of hepatitis B surface antigen (HBsAg) was 8.8% in 1979, 9.8% in 1992, and 7.2% in 2006, showing a declining trend that was most prominent in the population under 15 years of age.²⁻⁴ In comparison with 1992 survey, the 2006 national survey reported a significantly lower HBsAg prevalence among children less than 5 years old, reducing from 9.7% to 1.0%, probably mainly due to the increasing vaccination coverage during the past 10 years. It is also interesting to note that the prevalence of hepatitis B core antibody (anti-HBc), a marker of past infection, among adults in 2006 remained almost unchanged compared to the corresponding groups in 1992 that were 10-15 years younger, suggesting a low rate of HBV transmission among Chinese adults since 1990s.²⁻⁴

Despite these achievements, challenges remain. In 1992, 46% of the population surveyed within age of 6-10 years had been infected, and 10% were chronic carriers. This epidemic will continue to impact this generation and result in heavy disease burdens. HBV will continue to be the most common chronic infection among Chinese adults in the visible future, leading to millions of cases of cirrhosis and liver cancer if not adequately treated. In addition, the variation of HBV prevalence by demographic characteristics needs to be better understood. For instance, men were more likely to become HBsAg positive than women (8.6% *versus* 5.7%, $P < 0.01$), and people living in western region had higher HBsAg seropositive rates than those living in eastern region (8.3% *versus* 6.5%, $P < 0.05$). The variation between ethnic groups was

marked, with the highest rate of 13.4% reported in the Zhuang minority, and the lowest rate of 2.1% in the Mongolian population.² Since these variations are likely related to the inequality of health care access and services, barriers to accessing vaccination and other preventive modalities among populations with higher prevalence should be assessed and addressed.

Acute hepatitis

Although acute viral hepatitis is one of notifiable infectious diseases in China, the uncertainty regarding the quality of case identification and underreport rate make it difficult to evaluate reported data.⁵ Large-scale active surveillances conducted in the 1990s reported high incidences of acute viral hepatitis in China, ranging from 146-188 cases per 100 000 person-years.^{6,7} In hospital-based studies, hepatitis A and B were the most common pathogens identified, accounting for 44% and 26% of cases, respectively. For patients greater than 40 years old, hepatitis B was the most common cause of acute hepatitis. Symptomatic cases are uncommon in children. Based on the four-year experience of a pediatric medical center in Beijing in 1990s, only 5% of acute viral hepatitis cases in children under 14 years were caused by HBV.⁸ Although lacking recent data, it is likely that incidence of acute hepatitis B has been significantly reduced in the past decade due to the national vaccination program and improved health care overall.

Previous studies have also shown that exacerbation of chronic hepatitis B is sometimes misdiagnosed as acute hepatitis, which occurred commonly in areas with high HBV endemicity.⁹ Patients with either true acute hepatitis B or a flare of previously asymptomatic chronic HBV infection may present with an abrupt onset of illness. While the former are usually found to be anti-HBc IgM positive, the later may be either anti-HBc IgM positive or negative.¹⁰ In a study by Wang *et al*,¹¹ anti-HBc IgG was present in 24 of 48 Chinese patients diagnosed as acute hepatitis B by clinical manifestation and positive anti-HBc IgM. During the 8-17 months' follow-up period, patients with initial positive anti-HBc IgG did not experience HBsAg seroconversion, however, 8 (33%) had recurrence of hepatitis. In comparison, all patients with negative anti-HBc IgG experienced HBsAg seroconversion and none had recurrence. Given the existent pool of chronic HBV infections and reduced HBV transmission among Chinese adults, we hypothesize that flares of chronic HBV may account for a large proportion of reported 'acute hepatitis B' cases and suggest caution to clinicians on this phenomenon. To further elucidate this question, pathological investigation is required.

Chronic liver diseases

Chronic liver diseases including chronic hepatitis, cirrhosis, and liver cancers have been among the leading causes of death in the Chinese population. As it takes decades to see the long-term effect of vaccination programs, the current picture may be similar to the 1990s. Vital statistical data in 2010 showed that mortality in China from cirrhosis and chronic hepatitis was 11.7 per 100 000 person-years, and mortality from primary liver cancer was 24.8 per 100 000 person-years. Together, these liver diseases are responsible for 5.1% of deaths in mainland China.¹² Based on this data, HBV alone accounts for around 4% of total mortality among the Chinese population. HBsAg carrier status is associated with a 27% increase of overall mortality and 23 times higher risk of death from chronic liver diseases.

Chronic hepatitis Millions of Chinese are impacted by chronic hepatitis due to HBV. The prevalence of chronic hepatitis caused by HBV was approximately 1%, when diagnosis was based on positive HBsAg and elevated alanine transferase (ALT).¹³ For patients with biopsy-proven chronic hepatitis B, the overall mortality rate was 4.5 folds of the general population.¹⁴ In hospital-based prevalence studies, approximately 75% of patients with chronic hepatitis were HBsAg positive, whereas hepatitis C virus (HCV) was found in less than 10% of cases.¹⁵⁻¹⁷

Cirrhosis The positive rate of HBsAg in Chinese patients with cirrhosis ranged from 44% to 91%, with most studies reporting a prevalence of 70% or higher.^{15, 16, 18} Biopsy-based studies were in line with serological studies, with HBsAg detected in 79% of cases.¹⁹ Among patients with cirrhosis, the prevalence of HCV markers including anti-HCV antibody and HCV-RNA varied among different studies, ranging from 5% to 43%. The prevalence of co-infection of both HBV and HCV in patients with cirrhosis varied from 4% to 29%.^{15, 18} Since a considerable proportion of Chinese patients with cirrhosis had experienced secondary gastrointestinal bleeding and subsequent therapeutic blood transfusion,²⁰ through which they may have contracted HCV infection, in such cases, HCV transmission may have occurred after cirrhosis. In addition, HBV DNA was detectable in 23% to 39% of HBsAg negative cirrhotic patients, suggesting a role of occult HBV infection in the development of cirrhosis.²¹

Several other causes of cirrhosis in China have been studied. A pathological study reported that in HBsAg positive cirrhosis 13% were also positive under hepatitis delta virus (HDV) antigen staining.²² And 7% of cases of cirrhosis were attributed to alcohol from a large survey including 719 cases.²³ However, a study in Tibet found that 60% of

cirrhosis was caused by excessive alcohol intake.²⁴ In middle regions of China where schistosomiasis was prevalent, up to 18% of cases of cirrhosis resulted from this pathogen.²⁵

HCC HCC is the second most common type of malignancy in China, following lung cancers. Approximately 70%-80% of HCC in China occurred among patients with chronic HBV infection.¹ Age, gender, and residence are major demographic factors that are associated with HCC in China. The age-specific pattern of HCC incidence varied in different areas. In Qidong and Fusui, where HCC occurred at a high rate, the incidence increased sharply between the ages of 30 and 55, and then declined steadily with age;²⁶ whereas in Shanghai, the rising incidence began at age 50 and transitioned to a stable rate after age 70.²⁷ Incidences in men were 2.2 to 3.6 times higher than that in women. Geographic variation was marked, with the incidence varying from 18 to 105 per 100 000 person-years for male, and from 7 to 28 per 100 000 person-years for female.¹ HCC prevalence is higher in southeast coastal area. For instance, Tongan, Fusui, Qidong, and Haimen reported the highest rates of HCC, where many epidemiological studies were conducted.

Prospective studies, most of which were conducted in areas with high prevalence of HCC, reported the relative risk of chronic HBV infection for HCC ranging from 4 to 103, compared with HBsAg negative population.¹ Case-control studies in areas with low to moderate prevalence of HCC reported odds ratios for HBV infection ranging from 13 to 31.^{28, 29} In biopsy series, three quarters of liver tissues with HCC had detectable HBsAg, and cirrhosis existed in majority of cases.

Growing evidence suggests that aflatoxin is an important risk factor for HCC in China.³⁰ In Shanghai, approximately 50% of HCC cases were reported as possibly being related to aflatoxin exposure. This attributable proportion of aflatoxin for HCC is similar to that reported from Qidong (57%).³¹ The dose dependent association between aflatoxin and HCC is still controversial, as the gradient effect was observed in studies from Taiwan,³² but not from Qidong.³¹ In addition, a synergistic role between HBV and aflatoxin for the development of HCC has emerged over several studies: in HBsAg negative populations, the odds ratios of having HCC in populations with positive urinary aflatoxin metabolite or albumin aflatoxin adducts ranged from 0.3 to 1.9, while in HBsAg positive populations, the odds ratios were 3.3-12.5.^{33, 34} When calculating the relative risk of HBV in patients with HCC, however, few studies took into consideration the influence of aflatoxin. To accurately evaluate the attributable fraction of HBV for de-

velopment of HCC in China, we believe more researches are needed to further elaborate the role of aflatoxin in the pathogenesis of HCC in China.

HCV infection did not appear to be an important contributing factor in hyperendemic regions with HCC, since the prevalence of anti-HCV antibody was low among HCC cases (5% in Qidong and 1.5% in Haimen).^{35, 36}

HBV transmission

Perinatal and childhood transmission Although the national HBV vaccination program has significantly reduced both perinatal and childhood HBV transmission, better understanding of past HBV transmission among these groups is still valuable for the prevention HBV and other infections such as HCV and human immunodeficiency virus (HIV). It was estimated that around 3% of Chinese newborns in the 1990s were HBsAg positive. This estimation was based on the prevalence of HBsAg among women in reproductive age, among whom around a third were hepatitis B e antigen (HBeAg) positive.⁴

When HBV vaccination was not widely available, infection rate from HBV in early childhood (1-5 years) was high. Perinatal transmission alone could not explain a HBsAg prevalence of 10% in early childhood in Chinese population reported from 1992 national survey. Liu *et al*³⁷ followed 448 HBV-susceptible children aged 3-5 years for one year, and found that 9.2% of them became infected by HBV, and 3.8% of them became HBsAg carriers. Intra-familial transmission, horizontal transmission, and unsafe injection were suspected to be the major contributors of transmission in this age group; unfortunately, no studies have evaluated these transmission routes concurrently and therefore it is difficult to accurately assess bias and interactions between these routes of transmission. HBsAg positive parents were associated with 2-5 times increased risk of HBsAg positivity in their children. Liu *et al*³⁷ have reported that the infection rate among susceptible children was significantly higher in classes with higher prevalence of HBsAg, pointing to interpersonal contact as another important transmission route. Although relevant data regarding iatrogenic transmission are limited, the impact of this transmission should not be underestimated. A study conducted in the 1980s reported that the overall HBV infection rate dropped by 65% in one year-old children with after implementation of stringent practices to sterilize needles, re-usable syringes, and acupuncture equipment.³⁸

Transmission in adults Several studies based on symptomatic acute cases diagnosed in hospitals reported that having contact with patients with known hepatitis B

(18%-55%) and history of injection, transfusion, and operation (12%-65%) were major risk factors for HBV infection of Chinese adults.^{39, 40} To evaluate intrafamilial sexual transmission, Fang and coworkers⁴¹ followed 57 susceptible adults with HBsAg positive spouse for 2 years and found that 8 (14%) of them became HBsAg positive and 30 (53%) of them were infected. In comparison, for the families where both partners were initially uninfected, 2% (2/122) of subjects became HBsAg positive and 16% (20/122) were infected at the end of the study. Having a HBsAg positive spouse was associated with an 8.6 times risk of becoming chronic HBV infected for the sero-negative partner, and 3 times risk for HBV infection.⁴¹ Finally, tattooing-associated HBV transmission has been reported by a study in Taiwan.⁴²

HBV treatment

With the development of China's economy and health care system, more HBV medications and testing assays have become available for patients which have improved the quality of HBV treatment and care.⁴³ During 2006-2010, the National Plan for Prevention and Treatment of Hepatitis B was adopted and implemented, reflecting the commitment of the Chinese Ministry of Health to tackling the challenge of HBV.¹ The National Plan included public health strategies, treatment guidelines, and the initiation of nationwide educational programs.⁴⁴ Strong momentum has been maintained in the research field, especially for conducting and participating in national and international clinical trials.⁴⁵ Research has shown that treatment efficacy among Chinese patients is generally comparable to those reported from industrialized countries. In public health sector, several medications for HBV treatment have been included in the National Reimbursement Catalogue for Drugs of Basic Medical Insurance, which paved the way for the further adoption by local governments.⁴⁵ Currently, interferon-alfa, peginterferon alfa-2a, lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir are approved and marketed in China. To accelerate the translation of policy and scientific advances into patient benefits in the real world, however, transitional research and implementation science needs to be emphasized and strengthened to guide the public health strategies. Specifically, HBV treatment coverage should be evaluated, barriers of adherence should be identified, and interventions should be explored to improve the quality of treatment.

Conclusions

National vaccination program has started to reverse HBV

epidemic in China, leading to significant reduction of HBV infection among Chinese children. However, chronic liver diseases caused by HBV will be continuously representing a major public health challenge in China during following decades, leading to heavy disease burdens among current generation. The future of the battle against HBV in China will rest upon not only the persistent effort to further expend the vaccination program, but also the successful implementation of HBV treatment programs.

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